A 947B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/444,790	05/19/1995	MANFRED BROCKHAUS	9189	5612

37500 7590 04/03/2006

AMGEN INC.
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

RECEIVED
APR 06 2006
AMGEN LAW DEPARTMENT

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/03/2006

Docketed: 7-3-06

Please find below and/or attached an Office communication concerning this application or proceeding.

Docketed: Respond to OA
Review: SMO 7.3.06
Due Date: 6MO 10.3.06
By: VP

RECEIVED
APR 12 2006
MARSHALL GERSTEIN

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	08/444,790	BROCKHAUS ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,66,67,102-107,110-114 and 119-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,66,67,102-107,110-114 and 119-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 May 1995* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/05, 2/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Zachary C. Howard, Art Unit 1646, Technology 1600.

Status of Application, Amendments and/or Claims

The amendment of 10/5/05 and the supplemental amendments of 12/14/05 and 2/21/06 have been entered in full. In the 10/5/05 amendment, claims 62, 66, 102, 104-110 and 112-114 are amended. Claims 63-65, 68-101, 108, 109 and 115-118 are canceled. New claims 119-138 are added. In the 12/14/05 amendment, claims 102-105, 112, 113, 123, 124, 132 and 133 are amended, and new claim 138 is added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 62, 66, 67, 102-107, 110-114 and 119-138 are under consideration in the instant application.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 3/28/2005 and 2/21/2006 have been considered by the examiner.

The information disclosure statement filed 12/20/05 fails to comply with 37 CFR 1.98(a)(5), which requires the following: "a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered." The IDS filed 12/20/05 lacks a heading clearly indicating that the list is an information disclosure statement. As stated in MPEP 609 [R-3]: "Information submitted to the Office that does not comply with the requirements of 37 CFR 1.97 and 37 CFR 1.98 will not be considered by the Office but will be placed in the application file."

Priority

(1) In view of the papers filed 2/21/2006, European Patent Application No. 99100703.0, filed August 31, 1990, is added to the foreign priority claim of the present application (under 35 USC 119 (a-d)). Applicants have submitted a Request to Correct the Filing Receipt. The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the priority as corrected.

(2) It is noted that the Foreign Applications SWITZERLAND 3319/89 09/12/1989 and SWITZERLAND 746/90 03/08/1990, to which the present application claims priority, do not disclose the sequence of SEQ ID NO: 4. It is further noted that the Foreign Application SWITZERLAND 1347/90 4/20/1990, to which the present application claims priority, does not disclose the exact sequence of SEQ ID NO: 4. Rather, 1347/90 discloses an amino acid sequence in Figure 4 that differs from SEQ ID NO: 4 at residue 3. 1347/90 has a 'Ser' at residue 3 in Figure 4 while instant SEQ ID NO: 4 has a 'Thr' at residue 3. In the papers filed 1/18/2005, Applicants stated, "Applicants note that SEQ ID NOs: 3 and 4 are identical to Figure 4 except they also include the sequence correction noted at page 35, lines 32-36 of Example 8 (amino acid at position 3 is Thr instead of Ser as it is encoded by "ACC" not "TCC")" (pg 14). However, Example 8 of 1347/90 does not appear to disclose this correction. Therefore, with regard to sequences comprising the entirety of SEQ ID NO: 4, the instant application does not merit priority to the filing date of 1347/90.

Furthermore, 1347/90, while disclosing a partial sequence of the extracellular region of TNF2R (Figure 4), does not appear to disclose fusion proteins comprising TNF2R and "all of the domains of the constant region of a human immunoglobulin heavy chain other than the first domain of said constant region" (as set forth in the claims). Support for this limitation is set forth in the instant application at pg 11, lines 1-10, as noted by Applicants in the 1/18/05 response when the limitation was added to the claims. However, the 1347/90 application does not appear to disclose this information.

It is further noted that Foreign Application EPO 99100703.0 8/31/1990, to which the present application also claims priority, does appear to disclose SEQ ID NO: 4 (in

the form of Figure 4 and the amino acid change at residue 3 noted in Example 8), and fusions of said sequence with the constant region of a human immunoglobulin heavy chain other than the first domain of said constant region. Therefore, with regard to fusion proteins comprising the sequence of SEQ ID NO: 4 and "all of the domains of the constant region of a human immunoglobulin heavy chain other than the first domain of said constant region", the instant application is entitled priority to 8/31/1990, which is the filing date of EPO 99100703.0.

Specification

The disclosure is objected to because of the following informalities:

(1) An updated priority statement of the instant application's parent provisional and nonprovisional applications should be included in the first sentence of the specification or application data sheet. This priority statement was last updated in the preliminary amendment of 5/19/1995. Specifically, this statement should be amended to indicate that application 08/095,640 has been issued as U.S. Patent 5,610,279 (7/21/1993) and also that application 07/580,013 has been abandoned.

(2) The title of the invention ("HUMAN TNF RECEPTOR") is not descriptive because the claims are all directed to a human TNFR immunoglobulin fusion protein. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "HUMAN TNF RECEPTOR IMMUNOGLOBULIN FUSION PROTEIN."

Appropriate correction is required.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (4/5/2005).

All rejections of claims 63, 65, 68-71, 75-77, 100, 101, 108, 109 and 115-118 are *withdrawn* in view of Applicants' cancellation of the claims.

The rejection at pg 2-4 of claims 62, 66, 67, 102-107, 110-114 and 119-137 under the judicially created doctrine of obviousness type double patenting as being

obvious over claims 1 and 4 of U.S. Patent No. 5,610,279 is *withdrawn* in view of Applicants' amendments to the claims.

The rejection at pg 5 of claims 62, 66, 67, 102-107, 110-114 and 119-137 under 35 U.S.C § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' arguments.

Please see new claim rejections, below.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

Claims 123, 124, 132 and 133 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel biological materials. Specifically, new claims 123, 124, 132 and 133 claim proteins comprising the constant region of the human immunoglobulin heavy chain encoded by the plasmids pCD4Hγ1 or pCD4Hγ4. Since the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C § 112 may be satisfied by a deposit of the biological materials. It is noted that the specification indicates (pg 17, lines 25-31) that pCD4Hγ1 and pCD4Hγ4 have been deposited at the Deutschen Sammlung von Mikroorganism (DSM) in Braunschweig, FRG as accession numbers DSM5314 and DSM5523. Applicants have deposited the biological materials (p. 17 of the specification). However, there is no indication in the specification as to public availability.

If a deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicant(s) or person associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the

Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R.§1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, should be submitted stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 C.F.R.§1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 C.F.R.§1.809(d) should be added to the specification. See 37 C.F.R.§§ 1.803-1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 62, 66, 67, 102-107, 110-114 and 119-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35

U.S.C. § 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

The claims are genus claims because the claims are directed to variant polypeptides that specifically bind human TNF. The polypeptides comprise two parts: (a) a soluble fragment of a receptor; and (b) "all of the domains of the constant region of a human immunoglobulin heavy chain other than the first domain of said constant region". In claim 62, part (a) encompasses a protein comprising any soluble fragment of receptor comprising a fragment of SEQ ID NO: 4. The sequence of SEQ ID NO: 4 consists of 392 amino acids (also shown in Figure 4) and represents a partial sequence of the full-length human tumor necrosis factor type II receptor (TNF-IIR or TNF2R; also known variously as p75 or p80 based on the molecular weight on a SDS-polyacrylamide gel). The full-length mature human TNF2R is 439 amino acids, with the extracellular portion consisting of amino acids 1-235 (see pg 233 and Figure 1 of Dembic et al, 1990. Cytokine. 2(4): 231-7). Instant SEQ ID NO: 4 represents only a portion of the full-length TNF2R sequence; specifically, instant SEQ ID NO: 4 is missing amino acids 1-48 found in the full-length mature TNF2R. Therefore, instant SEQ ID NO: 4 is missing the first 48 amino acids of the extracellular domain (approximately 20% of the extracellular domain). Applicants further disclose a sequence consisting of 17 of the 18 N-terminal amino acids of the full-length TNFR2 (see pg 33; SEQ ID NO: 10). Together, SEQ ID NO: 4 and 10 consist of only a portion of the TNF2R extracellular domain (residues 1-7, 9-18 and 49-235).

The relevant art teaches that the extracellular domain of human TNF2R is the portion of the protein that binds human TNF. Chan et al teaches, "The deletion of PLAD [protein-ligand assembly domain] from either p60 or p80 completely abrogated ligand binding (Table 1 and Fig. 1E)" (pg 2351 of Chan et al. 2000, Science, 288: 2351-2354). Chan teaches that the PLAD is amino acids 10-54 of the receptor (pg 2351). Furthermore, specific single or double mutations in this region in the TNFRI receptor

"eliminated TNF-α binding" (pg 2351). Chan concludes "the PLAD is physically distinct from the ligand contact domain but nonetheless essential for efficient TNF-α binding and receptor function." In view of the teachings of Chan, the truncated receptor of SEQ ID NO: 4 taught by Applicants would not have the ability to bind TNF, as required by the claims.

The claimed protein comprises any soluble fragment of TNFR2 that comprises any fragment of SEQ ID NO: 4. Therefore, this fragment can be as long as the entire extracellular domain (comprising the entirety of SEQ ID NO: 4), or it can be as small as one amino acid from SEQ ID NO: 4. However, Applicants do not teach any amino acid sequence that can actually bind TNF. Applicants do not disclose any teachings demonstrating that SEQ ID NO: 4 (missing 48 amino acids of the extracellular domain of TNFR2) can bind to TNF. Therefore, the specification has not described a single example of a protein in the claimed genus that can actually bind human TNF.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of any member of the genus of claimed polypeptides. Neither the specification nor the claims describe a TNF2R protein sequence that can bind to TNF-α. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the instant claims do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62, 66, 67, 102-107, 110-114, 119-122, 125-131 and 134-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dembic et al (Cytokine, Vol. 2, No. 4 (July) 1990: 231-237) in view of Capon et al, U.S. Patent No. 5,116,964, published 26 May 1992 and filed 22 November 1989.

As noted above, in the section titled "Priority", 31 August 1990 is the earliest date for which the claimed protein comprising SEQ ID NO: 4 and Ig domains is entitled priority.

Claims 62, 66, 67, 102-107, 110-114, 119-122, 125-131, 134-136 and 138 each encompass a genus of variant polypeptides. While the scope of each genus varies, each encompasses the following polypeptide: a purified protein, recombinantly produced in CHO cells, that specifically binds human TNF and comprises parts (a) and (b).

Part (a) of each claim encompasses a soluble fragment of a receptor; wherein the receptor has three characteristics: (i) binds TNF; (ii) 75 kDa molecular weight; and (iii) "comprises a fragment of the amino acid sequence set forth in SEQ ID NO: 4" or "is encoded by a nucleic acid sequence comprising a fragment ... of SEQ ID NO: 3" (SEQ ID NO: 3 encodes SEQ ID NO: 4). Characteristic (iii) encompasses any sequence comprising any fragment of SEQ ID NO: 4; that is, comprising any shorter sequence found within the sequence of SEQ ID NO: 4. In other words, any longer sequence that includes a shorter sequence found within SEQ ID NO: 4 meets the limitation of a fragment that comprises a "fragment of the amino acid sequence set forth in SEQ ID NO: 4" or "encoded by a nucleic acid sequence comprising a fragment ... of SEQ ID NO: 3" (because SEQ ID NO: 4 is encoded by SEQ ID NO: 3). The narrowest claims also include the limitation that the soluble fragment comprises the following peptides: LCAP, VFCT, and peptide LPAQVAFXPYAPEPGSTC (wherein X is any amino acid as taught on pg 33 of the specification); however, each of the claims encompasses a protein including these three peptides.

Part (b) of each claim encompasses "all of the domains of the constant region of a human immunoglobulin heavy chain other than the first domain of said constant

region". The narrowest claims limit immunoglobulin heavy chain to human IgG1; however, all of the claims encompass this limitation.

Dembic teaches the full-length amino acid sequence of the 75kDa Tumor Necrosis Factor receptor (see pg 232 and Figure 1). This receptor meets the three characteristics of the receptor of claim 62: (i) it binds TNF; (ii) 75kDa; and (iii) comprises a numerous fragments of the sequence set forth in SEQ ID NO: 4. Furthermore, as shown in Figure 1, the sequence taught by Dembic comprises the following peptides within the extracellular domain: LCAP (residues 114-117), VFCT (residues 43-47) and peptide LPAQVAFXPYAPEPGSTC (residues 1-18; this peptide meets the sequence LPAQVAFXPYAPEPGSTC). Dembic further teaches the extracellular domain of this receptor forms a soluble fragment that binds TNF (see pg 234, column 1).

Dembic does not teach a fusion of the extracellular domain of the 75 kDa TNF receptor with any portion of the constant region of a human immunoglobulin heavy chain.

Capon teaches (Example 4, starting at column 40) a fusion of truncated murine lymphocyte homing receptor (MHLR) to the Fc region of human IgG1 ("These truncated proteins are all joined to a human heavy chain γ 1 region just upstream of the hinge domain (H) such that these chimeras contains the two cysteine residues of the hinge responsible for dimerization as well as the CH2 and CH3 constant regions." The Fc region consists of the CH2 and CH3 domains of the constant region but does not include the CH1 domain. Capon further teaches that the hybrid immunoglobulins can be used for affinity purification of ligands (col 22, lines 5-6). Capon further teaches Capon further teaches recombinant production of hybrid immunoglobulins in cell culture (col 26, lines 24-26). Capon further teaches that CHO cells are suitable eukaryotic cells for production of hybrid immunoglobulins (col 29, line 37). Capon further teaches purification of the hybrid immunoglobulin from cell cultures following expression in host cells (col 30, line 26-27). Capon further teaches placement of the purified hybrid immunoglobulin in "sterile, isotonic formulations" that are "preferably liquid" and "ordinarily a physiologic salt solution" (col 31, lines 4-8). Such solutions meet the definition of a "pharmaceutically acceptable carrier material" (as in claim 114).

It would be obvious to the person of ordinary skill in the art at the time the invention was made to fuse the extracellular portion of the TNF receptor sequence taught by Dembic to the Fc region taught by Capon, and to recombinantly produce the protein in CHO cells and purify the protein produced as taught by Capon. The person of ordinary skill in the art would be motivated to do so in order to produce and purify the TNF receptor-Ig fusion for use in affinity purification of the TNF ligand. The person of ordinary skill in the art would have expected success because Capon teaches that Ig fusions can be made with a wide variety of proteins, and teaches all of the techniques for recombinant production of hybrid immunoglobulins in CHO cells and purification of the produced protein.

With respect to claims 114 and 137, the recitation of "a pharmaceutical composition" in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight. Therefore, the claims encompass any composition comprising a recombinant protein of claims 62, 66, 107, 134 or 135 (claim 114) or claim 105 (claim 137) and a pharmaceutically acceptable carrier material. As described above, Capon teaches compositions comprising a hybrid immunoglobulin in a pharmaceutically acceptable carrier material. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to further include the hybrid TNF receptor-immunoglobulin in a pharmaceutically acceptable carrier material. The person of ordinary skill in the art would be motivated to do so in order to resuspend the hybrid immunoglobulin for use following purification. The person of ordinary skill in the art would have expected success because Capon teaches the necessary procedures for purification and resuspension of the hybrid immunoglobulin.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

LORRAINE SPECTOR
PRIMARY EXAMINER

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 8

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	J. Murphy Zach Howard
Attorney Docket Number	01017/40451B

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
ZH	A11	08/478,995	N/A	Lauffler, Leander et al.	
	A12	2003/064480	04-03-2003	Lauffler, Leander et al.	
	A13	4,593,002	01-11-1982	Dulbecco	
	A14	4,675,285	09-19-1984	Clark et al.	
	A15	4,729,326	03-08-1988	Richter	
	A16	4,769,326	09-06-1988	Rutler	
	A17	4,894,439	01-16-1990	Dorin et al.	
	A18	4,912,044	03-27-1990	Jacob et al.	
	A19	4,935,233	06-19-1990	Bell et al.	
	A20	4,963,354	10-06-1990	Shepard et al.	
	A21	4,965,271	10-23-1990	Mandell et al.	
	A22	5,055,447	10-08-1991	Palladino et al.	
	A23	5,073,627	12-17-1991	Curtis et al.	
	A24	5,075,222	12-24-1991	Hannum et al.	
	A25	5,098,702	03-24-1992	Zimmerman et al.	
	A26	5,098,833	03-24-1992	Lasky et al.	
	A27	5,118,500	06-02-1992	Hanel et al.	
	A28	5,136,021	08-04-1992	Dembinski et al.	
	A29	5,155,027	10-13-1992	Sledziewski et al.	
	A30	5,211,395	06-29-1993	Gero	
	A31	5,211,945	05-18-1993	Wallach et al.	
	A32	5,225,538	07-06-1993	Capon et al.	
	A33	5,258,498	11-02-1993	Huston et al.	
	A34	5,264,416	11-23-1993	Park et al.	
	A35	5,270,038	12-14-1993	Klimpel et al.	
	A36	5,336,603	08-09-1994	Capon et al.	
	A37	5,350,683	09-27-1994	Sims et al.	
	A38	5,359,032	10-25-1994	Dayer et al.	
	A39	5,447,851	09-05-1995	Beutler et al.	
	A40	5,455,165	10-03-1995	Capon et al.	
	A41	5,478,925	12-26-1995	Wallach et al.	
	A42	5,512,544	04-30-1996	Wallach et al.	
	A43	5,514,582	05-07-1996	Capon et al.	
	A44	5,599,905	02-04-1997	Mosley et al.	
	A45	5,605,690	02-25-1997	Jacobs et al.	
	A46	5,610,279	03-11-1997	Brockhaus et al.	
	A47	5,633,145	05-27-1997	Feldmann et al.	
	A48	5,639,597	06-17-1997	Lauffer et al.	
	A49	5,695,953	12-09-1997	Wallach et al.	
	A50	5,705,364	01-06-1998	Etcheverry et al.	
	A51	5,721,121	02-24-1998	Etcheverry et al.	
	A52	5,808,029	09-15-1998	Brockhaus et al.	
	A53	5,811,261	09-22-1998	Wallach et al.	
	A54	5,863,786	01-26-1999	Feldmann et al.	
	A55	5,945,397	08-31-1999	Smith et al.	
	A56	5,981,701	11-09-1999	Wallach et al.	

Examiner Signature	Zach Howard	Date Considered	3/2/06

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 8

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	~~J. Murphy~~ Zach Howard
Attorney Docket Number	01017/40451B

ZH	A57	6,143,866	11-07-2000	Brewer et al.		
	A58	6,165,476	12-26-2000	Strom et al.		
	A59	6,201,105	03-13-2001	Smith et al.		
	A60	6,541,610	04-01-2003	Smith		
	A61	6,541,620	04-01-2003	Brewer et al.		
	A62	6,572,852	06-03-2003	Smith et al.		
	A63	RE 36,755	06-27-2000	Smith et al.		

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
ZH	B17	AU 58976	01-24-1991	Synergen, Inc.		
	B18	EP 120694	10-03-1984	Boss et al.		
	B19	EP 227110	07-01-1987	Satoshi et al.		
	B20	EP 230574	08-05-1987	Ruddle		
	B21	EP 269455	06-01-1988	Ikeyama et al.		
	B22	EP 325262	07-26-1989	Seed		
	B23	EP 414178	02-27-1991	Seed		
	B24	EP 417563	03-20-1991	Brockhaus et al.		
	B25	EP 460846	12-11-1991	Sims et al.		
	B26	EP 471701	02-26-1992	Lemarie et al.		
	B27	EP 526452	02-10-1993	Capon et al.		
	B28	EP 526905	02-10-1993	Wallach et al.		
	B29	EP 568925	11-10-1993	Wallach et al.		
	B30	EP 606869	07-20-1994	Wallach et al.		
	B31	GB 2 246 569	02-05-1992	Feldman et al.		
	B32	JP 02-154695	06-14-1990	Brockhaus et al.		
	B33	JP 61-293924	12-24-1986	Yojiro et al.		
	B34	WO 91/02078	02-21-1991	Rathjen et al.		
	B35	WO 91/08298	12-13-1991	Capon et al.		
	B36	WO 91/17184	11-14-1991	Carter		
	B37	WO 92/08495	05-29-1992	Gillies		
	B38	WO 92/13095	08-06-1992	Carmichael et al.		
	B39	WO 93/07863	04-29-1993	Mullarkey		
	B40	WO 93/19777	10-14-1993	Smith		
	B41	WO 94/06476	03-31-1994	Smith et al.		

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Exa	Cite	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book,

Examiner Signature	Zach Howard	Date Considered	3/2/06

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 8

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	~~J. Murphy~~ Z. Howard
Attorney Docket Number	01017/40451B

Examiner Initials	No.[1]	magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
ZH	C35	ABRAHAM et al., p55 Tumor Necrosis Factor Receptor Fusion Protein in the Treatment of Patients With Severe Sepsis and Septic Shock: ΔΔΔΔΔ JAMA, 19:1531-1538 (1997)	
	C36	ABRAHAM et al., Lenercept (p55 Tumor Necrosis Factor Receptor Fusion Protein) In Severe Sepsis and Early Septic Shock: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial With 1,342 Patients, Crit Care Med, 29:503-510 (2001)	
	C37	AGGARWAL et al., Characterization of Receptors for Human Tumour Necrosis Factor and Their Regulation by γ-Interferon, Nature, 318:665-667 (1985)	
	C38	AGGARWAL et al., Induction of Receptors for Tumor Necrosis Factor-α by Interferons Is Not a Major Mechanism for Their Synergistic Cytotoxic Response, J. Biol. Chem., 262:10000-10007 (1987)	
	C39	AGGARWAL et al., Human tumour necrosis factors: structure and receptor interactions, in Tumor necrosis factor and related cytotoxins, pp.. 39-51, (Ciba Foundation symposium 131), Wiley, Chichester (1987)	
	C40	ARENZANA-SEISDEDOS et al., Immunoregulatory Mediators in the Pathogenesis of Rheumatoid Arthritis, Scand. J. Rheumatol., Supplement 66:13-17 (1987)	
	C41	ARUFFO et al., Molecular Cloning of a CD28 cDNA by a High-Efficiency COS Cell Expression System, Proc. Natl. Acad. Sci. USA, 84:8573-8577 (1987).	
	C42	ASHKENAZI et al., Protection Against Endotoxic Shock by a Tumor Necrosis Factor Receptor Immunoadhesin, Proc. Natl. Acad. Sci., U.S.A. 88:10535-10539 (1991)	
	C43	AYALA, Modern Genetics, Benjamin/Cummings, Publ. Co., Menlo Park CA, p. 45. (1980)	
	C44	BAGLIONI et al., Binding of Human Tumor Necrosis Factor to High Affinity Receptors on HeLa and Lymphoblastoid Cells Sensitive to Growth Inhibition, J. Biol. Chem., 260:13395-13397 (1985)	
	C45	BENJAMINI et al., Antibody Structure, in Immunology: A Short Course, 3rd ed., Wiley-Liss New York, 61-69 (1996)	
	C46	BRANELLEC et al., TNF: Antitumoral Agent at the Border Lines of Immunity and Inflammation, Path. Biol., 39:230-239 (1991)	
	C47	BROCKHAUS et al., Identification of Two Types of Tumor Necrosis Factor Receptors on Human Cell Lines by Monoclonal Antibodies, Proc. Natl. Acad. Sci. USA, 87:3127-3131 (1990)	
	C48	CARTER et al., Purification, Cloning, Expression and Biological Characterization of an Interleukin-1 Receptor Antagonist Protein, Nature, 344:633-638 (1990)	
	C49	CARPENTER et al., Epidermal Growth Factor, J. Biol. Chem., 265:7709-7712 (1990)	
	C50	CARPENTER, Receptors For Epidermal Growth Factor And Other Polypeptide Mitogens, Ann. Rev, Biochem., 56:881-914 (1987)	
	C51	CASADEI et al., Expression and Secretion of Aequorin as a Chimeric Antibody by Means of a Mammalian Expression Vector, Proc. Natl. Acad. Sci., U.S.A. 87:2047-2051 (1990)	
	C52	COFFMAN et al., The Role of Helper T Cell Products in Mouse B Cell Differentiation and Isotype Regulation, Immunol. Rev., 102:5-28 (1988)	
	C53	CREASEY et al., A High Molecular Weight Component of the Human Tumor Necrosis Factor Receptor is Associated With Cytotoxicity, Proc. Natl. Acad. Sci. USA, 84:3293-3297 (1987)	
	C54	DAYER, Chronic Inflammatory Joint Diseases: Natural Inhibitors of Interleukin 1 and Tumor Necrosis Factor α, J. Rheumatol. 18 (Suppl. 27): 71-75 (1991)	
	C55	DOWER et al., Human Cytokine Receptors, J. Clin. Immunol., 10:289-299 (1990)	
	C56	EISENBERG et al., Primary Structure and Functional Expression From Complementary DNA of a Human Interleukin-1 Receptor Antagonist, Nature, 343:341-346 (1990)	
	C57	ELLISON et al., The Nucleotide Sequence of A Human Immunoglobulin Cγ1 Gene, Nucleic Acids Res. 10(13): 4071-79 (1982)	
✓	C58	ESMON, The Roles of Protein C and Thrombomodulin in the Regulation of Blood Coagulation, J. Biol. Chem., 264:4743-4746 (1989)	

Examiner Signature	Zach Howard	Date Considered	2-20-06

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 8

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	~~J. Murphy~~ Z. Howard
Attorney Docket Number	01017/40451B

Do Not Print →

	~~C59~~	~~European Search Report for EP 97 12 0604, dated 3/9/98~~
3/1	C60	FELL et al., Genetic Construction And Characterization Of A Fusion Protein Consisting Of A Chimeric F(ab') With Specificity For Carcinomas And Human IL-2, J. Immunol., 146:2446-2452 (1991)
	C61	FERNANDEZ-BOTRAN et al., A Soluble, High-Affinity, Interleukin-4-Binding Protein Is Present in the Biological Fluids of Mice, Proc. Natl. Acad. Sci., 87:4202-4206 (1990)
	C62	FERNANDEZ-BOTRAN, Soluble Cytokine Receptors: Their Role in Immunoregulation, The FASEB Journal, 5:2567-2574 (1991)
	C63	FERRANTE et al., Inhibition of Tumour Necrosis Factor Alpha (TNF-α)-Induced Neutrophil Respiratory Burst by a TNF Inhibitor, Immunology, 72:440-442 (1991)
	C64	FISHER et al., Cloning And Expression Of Human Tissue Factor cDNA, Thrombosis Research, 48:89-99 (1987)
	C65	FOLEY et al., An Inhibitor of the Toxicity of Tumour Nectrosis Factor in the Serum of Patients With Sarcoidosis, Tuberculosis and Crohn's Disease, Clin. Exp. Immunol., 80:395-399 (1990)
	C66	FOMSGAARD et al., Preliminary Study on Treatment of Septic Shock Patients With Antilipopolysaccharide IgG from Blood Donors, Scand. J. Infect. Dis., 21:697-708 (1989)
	C67	GARCIA et al., High Sensitivity of Transgenic Mice Expressing Soluble TNFR1 Fusion Protein to Mycobacterial Infections: Synergistic Action of TNF and IFN-γ in the Differentiation of Protective Granulomas, Eur. J. Immunol., 27:3182-3190 (1997)
	C68	GASCOIGNE et al., Secretion of a Chimeric T-Cell Receptor-Immunoglobulin Protein, Proc. Natl. Acad. Sci USA, 84:2936-2940 (1987)
	C69	GEHR et al., Both Tumor Necrosis Factor Receptor Types Mediate Proliferative Signals In Human Mononuclear Cell Activation, J. Immunol., 149:911-917 (1992).
	C70	GILLIES et al., Targeting Human Cytotoxic T Lymphocytes To Kill Heterologous Epidermal Growth Factor Receptor-Bearing Tumor Cells, J. Immunol., 144:1067-1071 (1991)
	C71	GOODMAN, Identification of Antigenic Determinants, in Basic & Clinical Immunol., 24-25 (1982)
	C72	GOODMAN, Immunogenicity & Antigenic Specificity, in Basic & Clinical Immunol., 101-108 (1991)
	C73	GOODWIN et al., Molecular cloning and Expression of the Type 1 and Type 2 Murine Receptors for Tumor Necrosis Factor, Molecular and Cellular Biology, 11:3020-3026 (1991)
	C74	GRAY et al, Cloning and Expression of cDNA for Human Lymphotoxin, a Lymphokine With Tumour Necrosis Activity, Nature, 312:721-724 (1984)
	C75	GRUNDMANN et al., Characterization of cDNA Coding for Human Factor XIIIa, Proc. Natl. Acad. Sci. USA, 83:8024-8028 (1986)
	C76	HAAK-FRENDSCHO et al., Inhibition of TNF by a TNF Receptor Immunoadhesin, J. Immunol., 152:1347-1353 (1994)
	C77	HANNUM et al., Interleukin-1 Receptor Antagonist Activity of a Human Interleukin-1 Inhibitor, Nature, 343:336-340 (1990)
	C78	HEFLIN et al., Prevention by Granulocyte Depletion of Increased Vascular Permeability of Sheep Lung Following Endotoxemia, J. Clin. Invest., 68:1253-1260 (1981).
	C79	HIMMLER et al., Molecular Cloning and Expression of Human and Rat Tumor Necrosis Factor Receptor Chain (p60) and Its Soluble Derivative, Tumor Necrosis Factor-Binding Protein, DNA and Cell Biology, 9:705-715 (1990)
	C80	HOBART, The Immune System: A Course on the Molecular and Cellular Basis of immunity, Blackwell Scientific Pubs, Page 7 (1975)
	C81	HOLTMANN et al., Down Regulation of the Receptors For Tumor Necrosis Factor By Interleukin 1 and 4β-Phorbol-12-Myristate-13-Acetate, J. Immunol., 139:1161-1167 (1987)
	C82	IDZERDA et al., Human Interleukin 4 Receptor Confers Biological Responsiveness And Defines A Novel Receptor Superfamily, J. Exp. Med., 171:861-873 (1990)
✓	C83	IMAMURA et al., Expression Of Tumor Necrosis Factor Receptors On Human Monocytes And Internalization Of Receptor Bound Ligand, J. Immunol., 139:2989-2992 (1987)

Examiner Signature	Zach Howard	Date Considered	2-2-06

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 5 of 8

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	J. Murphy Z. Howard
Attorney Docket Number	01017/40451B

34	C84	ISHIKURA et al., Differential Biologic Effects Resulting From Bimodal Binding of Recombinant Human Tumor Necrosis Factor to Myeloid Leukemia Cells, Blood, 73:419-424 (1989)
	C85	ISRAEL et al., Binding Of Human TNF-α To High-Affinity Cell Surface Receptors: Effect Of IFN, Immunology Letters, 12:217-224 (1986)
	C86	JACOBS et al., Pharmacokinetic Parameters and Biodistribution of Soluble Cytokine Receptors, International Review of Experimental Pathology, 34B:123-135 (1993)
	C87	JONES et al, Structure of Tumour Necrosis Factor, Nature, 338:225-228 (1989)
	C88	KACZMARSKI et al., The Cytokine Receptor Superfamily, Blood Reviews, 5:193-203 (1991)
	C89	KAUSHANSKY, Structure-Function Relationships of the Hematopoietic Growth Factors, Proteins: Structure, Function & Genetics, 12:1-9 (1992)
	C90	KEEGAN et al., The Interleukin-4 Receptor: Signal Transduction by a Hematopoietin Receptor, Journal of Leukocyte Biology, 55:272-279 (1994)
	C91	KEEGAN et al., Interleukin 4 Receptor: Signaling Mechanisms, Immunology Today, 15:423-432 (1994)
	C92	KLEINAU et al., Importance of CD23 for Collagen-Induced Arthritis: Delayed Onset and Reduced Severity in CD23-Deficient Mice, J. Immunol., 162:4266-4270 (1999)
	C93	KLINKERT et al., TNF-α Receptor Fusion Protein Prevents Experimental Auto-Immune Encephalomyelitis and Demyelination in Lewis Rats: an Overview, The Journal of Neuroimmunology, 72:163-168 (1997)
	C94	KOHNO et al., A Second Tumor Necrosis Factor Receptor Gene Product Can Shed a Naturally Occurring Tumor Necrosis Factor Inhibitor, Proc. Natl. Acad. Sci. USA, 87:8331-8335 (1990)
	C95	KRUSE et al., Conversion of Human Interleukin-4 Into a High Affinity Antagonist by a Single Amino Acid Replacement, The EMBO Journal, 11:3237-3244 (1992)
	C96	KULL et al., Cellular Receptor for ^{125}I-Labeled Tumor Necrosis Factor: Specific Binding, Affinity Labeling, and Relationship to Sensitivity, Proc. Natl. Acad. Sci. USA, 82:5756-5760 (1985)
	C97	LANDOLFI, A Chimeric IL-2/Ig Molecule Possesses The Functional Activity Of Both Proteins, J. Immunol., 146:915-919 (1991)
	C98	LANGNER et al., Structural and Functional Analysis of a TNF Receptor-Immunoglobulin Fusion Protein, New Advances on Cytokines, 349-354 (1992)
	C99	LEBERTHON et al., Enhanced Tumor Uptake of Macromolecules Induced by a Novel Vasoactive Interleukin 2 Immunoconjugate, Cancer Research, 51:2694-2698 (1991)
	C100	LESSLAUER et al., Recombinant Soluble Tumor Necrosis Factor Receptor Proteins Protect Mice From Lipopolysaccharide-Induced Lethality, Eur. J. Immunol., 21:2883-2886 (1991)
	C101	LIABAKK et al., A Rapid and Sensitive Immunoassay for Tumor Necrosis Factor Using Magnetic Monodisperse Polymer Particles, Journal of Immunological Methods, 134:253-259 (1990)
	C102	LOETSCHER et al., Efficacy of a Chimeric TNFR-IgG Fusion Protein to Inhibit TNF Activity in Animal Models of Septic Shock, Endotoxin Research Series, 2:455-462 (1993)
	C103	LOETSCHER et al., Two distinct human TNF receptors: purification, molecular cloning and expression, in Tumor Necrosis Factor: Structure-Function Relationship and Clinical Application, (3rd International Conference
	C104	MALISZEWSKI et al., Cytokine Receptors And B Cell Functions: Recombinant Soluble Receptors Specifically Inhibit IL-1 and IL-4 Induced Cell Activities In Vitro, J. Immunol., 144:3028-3033 (1990)
	C105	MOHLER et al., Soluble Tumor Necrosis Factor (TNF) Receptors Are Effective Therapeutic Agents in Lethal Endotoxemia and Function Simultaneously as Both TNF Carriers and TNF Antagonists, J. Immunol., 151:1548-1561 (1993)
	C106	MORI et al., Attenuation of Collagen-Induced Arthritis in 55-kDa TNF Receptor Type 1 (TNFR1)-IgG1-Treated and TNFR1-Deficient Mice, J. Immunol., 157:3178-3182 (1996)
↓	C107	MORRISSEY et al., Molecular Cloning of the cDNA for Tissue Factor, the Cellular Receptor for the Initiation of the Coagulation Protease Cascade, Cell: 50:129-135 (1987)

Examiner Signature	Zach Howard	Date Considered	2-2-06

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 6 of 8

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	~~J. Murphy~~ Z. Howard
Attorney Docket Number	01017/40451B

ZM	C108	MORRISON, In Vitro Antibodies: Strategies for Production and Application, Annu. Rev. Immunol., 10:239-265 (1992)
	C109	MOSLEY et al., The Murine Interleukin-4 Receptor: Molecular Cloning and Characterization of Secreted and Membrane Bound Forms, Cell: 59:335-348 (1989)
	C110	NOVOTNY et al., A Soluble, Single-Chain T-Cell Receptor Fragment Endowed With Antigen-Combining Properties, Proc. Natl. Acad. Sci. USA, 88:8646-8650 (1991)
	C111	OKAYAMA et al., High-Efficiency Cloning of Full-Length cDNA, Molecular and Cellular Biology, 2:161-170 (1982)
	C112	OKAYAMA et al., A cDNA Cloning Vector That Permits Expression of cDNA Inserts in Mammalian Cells, Molecular and Cellular Biology, 3:280-289 (1983)
	C113	OLD, Tumor Necrosis Factor, 2nd Intl Conference on Tumor Necrosis Factor & Related Cytokines, Napa, CA, 1-30 (1989)
	C114	PABORSKY et al., Purification of Recombinant Human Tissue Factor, Biochemistry, 28:8072-8077 (1989)
	C115	PARRILLO, Pathogenetic Mechanisms of Septic Shock, New Eng. J. Med., 328:1471-1477 (1993)
	C116	PEETRE et al., A Tumor Necrosis Factor Binding Protein is Present in Human Biological Fluids, Eur. J. Haematol. 41:414-419 (1988)
	C117	PENNICA et al., Human Tumour Necrosis Factor: Precursor Structure, Expression and Homology to Lymphotoxin, Nature, 312:724-729 (1984).
	C118	PIGUET et al., Evolution of Collagen Arthritis in Mice is Arrested by Treatment With Anti-Tumor Necrosis (TNF) Antibody or a Recombinant Soluble TNF Receptor, Immunology, 77 (4):510-514 (1992)
	C119	REDFIELD et al., Secondary Structure and Topology of Human Interleukin 4 in Solution, Biochemistry, 30:11029-11035 (1991)
	C120	RUBIN, Binding Receptor Characters Zako and Expression, and Intracellular Events. 2nd Intl Conference on Tumor Necrosis Factor & Related Cytokines, Napa, CA, 94-96 (1989)
	C121	RUDDLE et al., An Antibody to Lymphotoxin and Tumor Necrosis Factor Prevents Transfer of Experimental Allergic Encephalomyelitis, J. Exp. Med., 172:1193-1200 (1990)
	C122	RUTKA et al., The Effects of Human Recombinant Tumor Necrosis Factor on Glioma-Derived Cell Lines: Cellular Proliferation, Cytotoxicity, Morphological and Radioreceptor Studies, Int. J. Cancer., 41:573-582 (1988)
	C123	SAXNE et al., Detection of Tumor Necrosis Factor α But Not Tumor Necrosis Factor β in Rheumatoid Arthritis Synovial Fluid and Serum, Arthritis & Rheumatism, 31:1041-1045 (1988)
	C124	SCALLON et al., Functional Comparisons Of Different Tumour Necrosis Factor Receptor/IgG Fusion Proteins, Cytokine, 7:759-770 (1995)
	C125	SCARPATI et al., Human Tissue Factor: cDNA Sequence and Chromosome Localization of the Gene, Biochemistry, 26:5234-5238 (1987)
	C126	SCHLEIFFENBAUM et al., The Tumor Necrosis Factor Receptor and Human Neutrophil Function, J. Clin. Invest., 86:184-195 (1990)
	C127	SCHNEE et al., Construction and Expression of a Recombinant Antibody-Targeted Plasminogen Activator, Proc. Natl. Acad. Sci. USA, 84:6904-6908 (1987)
	C128	SECKINGER et al., A Human Inhibitor Of Tumor Necrosis Factor α, J. Exp. Med. 167:1511-1516 (1988)
	C129	SHALABY et al., Receptor Binding and Activation of Polmorphonuclear Neutrophils by Tumor Necrosis Factor-Alpha, Journal of Leukocyte Biology, 41:196-204 (1987)
	C130	SHALABY et al., Binding and Regulation of Cellular Function by Monoclonal antibodies Against Human Tumor Necrosis Factor Receptors, J. Exp. Med. 172: 1517-1520 (1990)
✓	C131	SHEEHAN et al., Generation and Characterization of Hamster Monoclonal Antibodies That Neutralize Murine Tumor Necrosis Factors, Journal of Immunology, 142:3884-3893 (1989)

Examiner Signature	Zach Howard	Date Considered	2-2-06

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 8

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	~~J. Murphy~~ Z. Howard
Attorney Docket Number	01017/40451B

	C132	SHIN et al., Expression and Characterization of an Antibody Binding Specificity Joined to Insulin-Like Growth Factor 1: Potential Applications for Cellular Targeting, Proc. Natl. Acad. Sci., 87:5322-5326 (1990)
	C133	SIMS et al., cDNA Expression Cloning of the IL-1 Receptor, a Member of the Immunoglobulin Superfamily, Science, 241:585-589 (1988).
	C134	SIMS et al., Cloning the Interleukin 1 Receptor From Human T Cells, Proc. Natl. Acad. Sci., 86:8946-8950 (1989)
	C135	SMITH et al., The Active Form of Tumor Necrosis Factor Is a Trimer, J. Biol. Chem., 262:6951-6954 (1987)
	C136	SMITH et al., Blocking of HIV-1 Infectivity by a Soluble, Secreted Form of the CD4 Antigen, Science, 238:1704-1707 (1987)
	C137	SMITH et al., Multimeric Structure of the Tumor Necrosis Factor Receptor of HeLa Cells, J. Biol. Chem., 264:14646-14652 (1989)
	C138	SPICER et al., Isolation of cDNA Clones Coding for Human Tissue Factor: Primary Structure of the Protein and cDNA, Proc. Natl. Acad. Sci., 84:5148-5152 (1987)
	C139	STAINES et al., Collagen Arthritis-What Can It Teach Us?, British Journal of Rheumatology, 33:798-807 (1994)
	C140	STRADER et al., Structural Basis of β-Adrenergic Receptor Function, The FASEB Journal, 3:1825-1832 (1989)
	C141	SUGGS et al., Use of Synthetic Oligonucleotides as Hybridization Probes: Isolation of Cloned cDNA Sequences for Human β_2-Microglobulin, Proc. Natl. Acad. Sci. U.S.A., 78:6613-6617 (1981)
	C142	TAUBER et al., Toxicity in Neuronal Cells Caused by Cererospinal Fluid fFom Pneumococcal and Gram-Negative Meningitis, The Journal of Infectious Diseases, 166:1045-1050 (1992)
	C143	THOMA et al., Identification of a 60-kD Tumor Necosis Factor (TNF) Receptor as the Major Signal Transducing Component in TNF Responses, J. Exp. Med. 172: 1019-23 (1990)
	C144	TSUJIMOTO et al., Characterization and Affinity Crosslinking of Receptors for Tumor Necrosis Factor on Human Cells, Archives of Biochemistry and Biophysics, 249:563-568 (1986)
	C145	TSUJIMOTO et al, Interferon-γ Enhances Expression of Cellular Receptors for Tumor Necrosis Factor, J. Immunol., 136:2441-2444 (1986)
	C146	TSUJIMOTO et al, Tumor necrosis factor: specific binding and internalization in sensitive and resistant cells, Proc. Natl. Acad. Sci. 82: 7626-30 (1985)
	C147	ULICH et al., Intratracheal Administration of Endotoxin and Cytokines, Clinical Immunology & Immunopathology,, 72:137-140 (1994)
	C148	UNGLAUB et al., Downregulation of Tumor Necrosis Factor (TNF) Sensitivity Via Modulation of TNF Binding Capacity by Protein Kinase C Activators, J. Exp. Med. 166:1788-1797 (1987)
	C149	VAN DER POLL et al., Pretreatment with a 55-kDa Tumor Necrosis Factor Receptor-Immunoglobulin Fusion Protein Attenuates Activation of Coagulation, but not of Fibrinolysis, during Lethal Bacteremia in Baboons, The Journal of Infectious Diseases., 176:296-299 (1997)
	C150	VAN ZEE et al., Protection Against Lethal *Escherichia coli* Bacteremia in Baboons (*Papio anubis*) by Pretreatment With a 55-kDa TNF Receptor (CD120a)-Ig Fusion Protein, Ro 45-2081, J. Immunol., 156:2221-2230 (1996)
	C151	WALLACH et al., Soluble and Cell Surface Receptors for Tumor Necrosis Factor, Progress, Inflammation Research & Therapy, 51-57 (1991)
	C152	WALLACH et al., Cell surface and soluble TNF receptors, in Tumor Necrosis Factor: Structure-Function Relationship and Clinical Application, (3rd International Conference on Tumor Necrosis Factor and Related Cytokines, Makuhari, Chiba, Nov. 21-25, 1990), Osawa and Bonavida, eds., Basel, Karger, pp 47-57 (1992)
✓	C153	WILKS, The CD4 Receptor: Post Binding Events, Conformational Change and the Second Site, Molec. Aspects Med., 12:255-265 (1991)

Examiner Signature	Zach Howard	Date Considered	2-2-06

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006, OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 8 of 8

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	~~J. Murphy~~ Z. Howard
Attorney Docket Number	01017/40451B

RM	C154	YAMASAKI et al., Cloning and Expression of the Human Interleukin-6 (BSF-2/IFNβ 2) Receptor, Science, 241:825-282 (1988).		
	C155	YONEHARA et al., A Cell-Killing Monoclonal Antibody (Anti-Fas) to a Cell Surface Antigen Co-Downregulated With the Receptor of Tumor Necrosis Factor, J. Exp. Med., 169:1747-1765 (1989)		
✓	C156	YOSHIE et al., Binding and Crosslinking of ^{125}I-Labeled Recombinant Human Tumor Necrosis Factor to Cell Surface Receptors, J. Biochem., 100: 531-541(1986)		

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature	Zach Howard	Date Considered	2-2-06

PTO/SB/08a/b (07-05)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	08/444,790-Conf. #5612
Filing Date	May 19, 1995
First Named Inventor	Manfred Brockhaus
Art Unit	1646
Examiner Name	Z. Howard
Attorney Docket Number	01017/40451B

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
ZH	—	Official Communication relating to an Opposition in EP Application No. 99 100 703.0.	—

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature	Zach Howard	Date Considered	3/2/06

Notice of References Cited	Application/Control No. 08/444,790	Applicant(s)/Patent Under Reexamination BROCKHAUS ET AL.	
	Examiner Zachary C. Howard	Art Unit 1646	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,116,964	05-1992	Capon et al.	536/23.5
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Dembic et al, 1990. Cytokine. 2(4): 231-7.
	V	Chan et al. 2000, Science, 288: 2351-2354.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.